REMARKS

Claims 57-67 are pending in this application. Claim 57 is amended herein for clarity and to more particularly define the invention. Support for this amendment can be found in claim 57 as originally filed and throughout the specification. The specification makes clear the fact that the chimeric protein of the claims is bound to the surface lattice protein only as one independent protein binds to another (e.g., as in antigen-antibody binding). Thus, as used in the context of claim 57, it is clear that the binding interaction between the chimera and the surface lattice protein is in the nature of protein-protein binding only, and is not in the nature of a covalent bond. For example, see page 2, lines 4-10 of the specification, page 2, lines 25-27 of the specification, page 3, lines 17-18, page 7, lines 2-4 of the specification, page 13, lines 20-23 of the specification, and page 21, lines 15-19 of the specification. It is believed that no new matter has been added by this amendment. In light of this amendment and the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue. Applicants acknowledge that the drawings in this application are objected to by the Draftsperson under 37 C.F.R. § 1.84. Therefore, applicants will provide formal drawings upon allowance of the application.

Applicants appreciate having been granted the opportunity to interview this case telephonically with Examiners Cook and Li on October 2, 2002. Specifically, the language of claim 57 was discussed, with applicants making the point that the binding interaction between the chimera and the surface lattice protein of the claimed invention is in the nature of protein-protein binding only, and is not in the nature of a covalent bond. Therefore, as suggested by Examiner Li, applicants have amended claim 57 herein to recite "wherein said chimera is bound to the T4 surface lattice protein array." The following remarks more specifically address the issues discussed in the interview.

I. Objection to the Specification

The Office Action states that the disclosure is objected to because the first page of the specification is not numbered. Applicants respectfully point out to the Examiner that a correctly numbered replacement page was attached to applicant's January 2, 2002 response to the July 3, 2001 Office Action. Therefore, applicants believe this objection has been overcome and respectfully request its withdrawal.

II. Objection to Drawings

Applicants acknowledge that the drawings in this application are objected to by the Draftsperson under 37 C.F.R. § 1.84. According to the Office Action, applicant is required to submit a proposed drawing correction in reply to this Office Action. However, formal correction of the noted defect can be deferred until the application is allowed by the Examiner. See MPEP 608.02(2).

Applicants reiterate that they will provide formal drawings upon allowance of the application. With regard to a proposed drawing correction, applicants plan to provide appropriately labeled reproduction quality photographs of the gels in Figures 3, 4, 5, 7, 8, 9 and 10. Applicants will also provide better quality line drawings of Figures 1, 2 and 6.

III. Rejection Under 35 U.S.C. § 112, first paragraph

The Office Action states that claims 57-67 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. According to the Office Action, Applicant's proposed amendment to claim 57 wherein "is bound to" is replaced by "interacts with" introduces a claim limitation that does not have support in the instant disclosure.

As stated above, applicants discussed the language of claim 57, in detail, with Examiners Cook and Li. Applicants pointed out that the chimeric protein of the claims is bound to the surface lattice protein only as one independent protein binds to another (e.g., as in antigen-antibody binding). Thus, as used in the context of claim 57, it is clear that the binding between the chimera and the surface lattice protein is in the nature of protein-protein binding only, and is not in the nature of a covalent bond. Furthermore, as pointed out by applicants during the telephone interview, there are numerous references in the literature where the term "bound" is clearly used to refer to a protein-protein interaction For example, Subramanian et al. ("A monoclonal antibody to avidin dissociates quaternary structure and curtails biotin binding to avidin and streptavidin," *Arch. Biochem. Biophys.* 344: 281-8 (1997)) states that "[a]n anti-avidin mAb, viz, H12G4, is shown to release bound biotin in a dose-dependent manner from holoavidin and holostreptavidin and inhibit the binding of ligand to the two apoproteins"(see Abstract, attached). Another reference, Sato et al., ("A new method for studying the binding of human IgE to CD23 and the inhibition of this binding," *J. Immunol. Methods* 209:59-66 (1997)) describes "a binding assay by which only the specific binding of IgE to CD23 expressed on Epstein-Barr virus (EBV) transformed B-cell line, L-KT9 cells, can be detected" (see Abstract, attached). In Ren and Black ("Phage T4 SOC and HOC display of biologically active, full-length proteins on the viral capsid," *Gene* 215: 439-44 (1998)) the authors state that "the number of molecules of each protein (10-40) bound per phage and their activity suggest that proteins can fold to native conformation and be displayed by HOC and SOC to allow binding and protein-protein interactions on the capsid" (see Abstract, attached). It is noted that the peer reviewed article by Ren and Black describes the present invention, and that the use of the term "binding" to describe the interaction of the chimera and the surface lattice protein establishes that there is no confusion in the art regarding the meaning of "bound to" in the context of the present invention. Thus, the above-mentioned references show that the term "bound to," as used in the context of claim 57, would be clearly recognized by one of skill in the art as referring to protein-protein interaction and not as a covalent bond. There is no factual evidence given by the Office, and none found by applicants, that suggests any confusion in the art regarding the meaning of "bound to" in the context of the type of construct described and claimed by

applicants. Therefore, applicants believe that the language of herein amended claim 57 is clear and adequately supported in the specification. Thus, applicants believe this rejection has been overcome and respectfully request its withdrawal.

IV. Rejection Under 35 U.S.C. § 102(a)

The Office Action states that claims 57-67 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Ren et al. (Protein Science (1996), Vol. 5, pages 1833-1843). The Office Action also states that applicants will file a Katz-type declaration.

Applicants respectfully point out to the Examiner that a Katz Declaration was provided with the January 2, 2002 response to the July 3, 2001 Office Action. Furthermore, in the October 2, 2002 telephone interview, applicants pointed out to Examiner Cook that the Katz Declaration had been filed and that she had previously withdrawn this rejection. Examiner Cook indicated that this was, in fact, the case, and requested that applicants point this out in response to the outstanding Office Action.

V. Rejections Under 35 U.S.C. § 103(a)

The Office Action states that claims 57, 62, 63, 64, 66 and 67 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ladner et al. in view of MacDonald et al. The Office Action also states that claims 58, 59, 60, 61 and 65 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ladner et al., in view of MacDonald et al. and in further view of Aebi et al.

Applicants note that this rejection was discussed in a telephone interview with Examiner Cook on July 3, 2002. In that interview, Examiner Cook indicated that her concern with the art was based on her interpretation of the term "bound to" in applicants claims as meaning a covalent bond between the present chimera and the surface lattice protein. In that interview, applicants expressed the belief that, in the context of the present claims, the term "bound" would be recognized by one in the art as referring to a

protein-protein interaction and not to the covalent bond described in Ladner et al. Nevertheless, the Examiner suggested that applicants modify the terminology of the claims to address her concern. Now, based on the most recent interview and applicants' remarks above, applicants understand that the Patent Office recognizes that the present claims, as amended to recite "bound to," are not suggested by the cited combination of art. For clarity and emphasis, our previous remarks on this point are reiterated below.

Applicants reiterate that the Ladner et al. reference describes a method of phage display in which a molecule of interest is displayed directly on the surface of the phage. The molecule of interest is fused with an OSP, defined as an outer surface protein, e.g. coat protein of a phage or LamB from *E. coli*, which must pass through the secretion system of the phage in order to be displayed on the surface. An outer surface protein, as defined by Ladner et al., is not a dispensable polypeptide. Therefore, the Ladner et al. reference is an example of classic phage display where the molecule of interest is displayed as part of a chimeric surface lattice protein. In other words, in Ladner et al., the molecule of interest is not linked to a dispensable polypeptide that then binds with a surface lattice protein as in the present invention, nor does Ladner et al. suggest any use for a dispensable polypeptide, much less as a polypeptide for displaying a molecule of interest on phage. Furthermore, because the display system described by Ladner et al. involves passage of the chimeric outer surface protein comprising the molecule of interest through the secretory system of the phage, there are size limitations that prevent the molecule of interest from being, for example, a large polypeptide. Since the present invention bypasses the secretory system of the phage by employing a chimera comprising a molecule of interest and a dispensable polypeptide, wherein the chimera binds to surface lattice proteins, the size limitations associated with classic phage display, e.g. Ladner et al., are eliminated.

The present invention also allows the preparation of a chimera comprising a molecule of interest and a dispensable polypeptide which can then bind *in vitro* to separately isolated surface lattice proteins, as described throughout the specification.

Therefore, it is not necessary to produce recombinant phage for every desired molecule of interest as would be necessary utilizing the method of Ladner et al.

Applicants have also pointed out that the MacDonald et al. reference merely discloses the genetic location of three genes on the T4 phage genetic map. One of these genes, SOC (surface outer capsid), is a dispensable polypeptide, but there is no method or motivation stated or suggested for utilizing SOC to make any composition, much less any composition of the present invention.

With regard to the Aebi et al. reference, applicants reiterate that this reference merely discloses structural studies pertaining to dispensable polypeptides, but there is no suggestion or motivation that dispensable polypeptides, SOC and HOC, would be useful for linking to a molecule of interest for the purpose of displaying the molecule of interest. Therefore, prior to applicant's invention, there was no reasonable expectation that a dispensable polypeptide can be linked to a molecule of interest and still retain the ability to bind intact phage

Therefore, there is no suggestion or motivation in any of Ladner et al., MacDonald et al. or Aebi et al., alone or in combination, that would allow one of skill in the art to arrive at the present invention. Thus, applicants believe that this rejection has been overcome and respectfully request its withdrawal.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No additional fee is believed due. However, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No.14-0629.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Gwendolyn D. Spratt — Date: 12-20-02

MARKED-UP VERSION OF AMENDED CLAIM

57. (Twice amended) A composition containing a T4 surface lattice protein array and a chimera, wherein the chimera comprises a molecule of interest, a T4 dispensable polypeptide and a linker, wherein the linker links the molecule of interest to the T4 dispensable polypeptide and wherein said chimera [interacts with] is bound to the T4 surface lattice protein array.

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1: Arch Biochem Biophys 1997 Aug 15;344(2):281-8 Related Articles, Links

A monoclonal antibody to avidin dissociates quaternary structure and curtails biotin binding to avidin and streptavidin.

Subramanian N, Subramanian S, Karande AA, Adiga PR.

Department of Biochemistry and Centre for Reproductive Biology & Molecular Endocrinology, Indian Institute of Science, Bangalore.

An anti-avidin mAb, viz., H12G4, is shown to release bound biotin in a dose-dependent manner from holoavidin and holostreptavidin and inhibit the binding of ligand to the two apoproteins. The release of biotin by this mAb is accompanied by quenching of ligand-induced enhanced fluorescence of the FITC-avidin conjugate. In terms of mechanism of release of bound biotin, we demonstrate that on binding to the Fab fragment of the mAb, the native tetrameric holoavidin undergoes dissociation progressively with time to monomers with no bound biotin associated with the latter. Based on the immunoreactivity associated with defined overlapping fragments of avidin obtained by chemical cleavage, the epitope recognized by mAb H12G4 has been localized to residues 58-96 of the primary sequence. By pepscan method of epitope mapping, this mAb is shown to identify a minimal core sequence of 87RNGK90 in avidin and a corresponding sequence of 84RNAH87 in streptavidin.

PMID: 9264540 [PubMed - indexed for MEDLINE]

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1: Gene 1998 Jul 30;215(2):439-44

Phage T4 SOC and HOC display of biologically active, full-length proteins on the viral capsid.

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Department of Biochemistry, Molecular Biology, University of Maryland School of Medicine, Baltimore, MD 21201-1503, USA.

The T4 phage capsid accessory protein genes soc and hoc have recently been developed for display of peptides and protein domains at high copy number (Ren et al., 1996. Protein Science 5, 1833-1843; Ren et al., 1997. Gene 195, 303-311). That biologically active and full-length foreign proteins can be displayed by fusion to SOC and HOC on the T4 capsid is demonstrated in this report. A 271-residue heavy and light chain fused IgG anti-EWL (egg white lysozyme) antibody was displayed in active form attached to the COOH-terminus of the SOC capsid protein, as demonstrated by lysozyme-agarose affinity chromatography (>100-fold increase in specific titer). HOC with NH2-terminal fused HIV-I CD4 receptor of 183 amino acids can be detected on the T4 outer capsid surface with human CD4 domain 1 and 2 monoclonal antibodies. The number of molecules of each protein (10-40) bound per phage and their activity suggest that proteins can fold to native conformation and be displayed by HOC and SOC to allow binding and protein-protein interactions on the capsid.

PMID: 9714843 [PubMed - indexed for MEDLINE]

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1: J Immunol Methods 1997 Nov 10;209(1):59-66 Related Articles, Links

A new method for studying the binding of human IgE to CD23 and the inhibition of this binding.

Sato T, Konishi A, Yasuno S, Arai J, Kamei M, Bitoh M, Yamaguchi T.

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CD23, a low-affinity receptor for IgE (Fc epsilonRII), is a type II membrane-bound glycoprotein expressed on many hematopoietic cells, particularly activated B-cells. CD23 binds to IgE at a domain homologous to Ca2+-dependent (C-type) animal lectin. This paper describes a binding assay by which only the specific binding of IgE to CD23 expressed on Epstein-Barr virus (EBV)-transformed B-cell line, L-KT9 cells, can be detected. This assay is useful in the search for CD23 ligands among many chemical compounds, because it is easily carried out and does not require the use of any radiolabeled reagents. Using the assay, we investigated the inhibition of IgE binding to CD23 by fucose-1-phosphate which has been reported to inhibit the binding of sCD23 to IgE [Delespesse, G., Sarfati, M., Wu, C.Y., Fournier, S., Letellier, M., 1992. The low affinity receptor for IgE. Immunol. Rev. 125, 77.] and the binding of CD23 to CD21 [Pochon, S., Graber, P., Yeager, M., Jansen, K., Bernard, A.R., Aubry, T.-P., Bonnefoy, J.-Y., 1992. Demonstration of second ligand for the low affinity receptor for immunoglobulin E (CD23) using recombinant CD23 reconstituted into flourescent liposomes. J. Exp. Med. 176, 389.]. Although both alpha- and beta-L-fucose-1-phosphate/di(cyclohexylammonium) salt decreased the extent of IgE binding to CD23, the inhibitory effects were not due to alpha- or beta-L-fucose-1-phosphate but to cyclohexylamine. The inhibitory effect of cyclohexylamine was dose dependent and the effect was decreased when inhibition tests were carried out in the presence of a 10-fold excess of IgE. These results suggest that cyclohexylamine specifically interacts with the binding of CD23 and IgE.

PMID: 9448034 [PubMed - indexed for MEDLINE]

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